REMARKS

Claims 4, 6-9, and 16-18 are pending. Claim 17 is amended to correct a typographical error. No new matter has been added.

A supplemental Information Disclosure Statement is attached. The Examiner is respectfully requested to review the references and indicate that she has done so by initialing and returning to Applicants the Form SB/08/a.

35 U.S.C. § 112, first paragraph (written description)

Claims 4 and 6-9 remain rejected as failing to comply with the written description requirement. This is a new matter rejection.

The PTO maintains that "[t]he specification does not contemplate a limitation wherein the dsRNA is 21 nucleotides in length and consists of separate non-linked strands and hence does not provide support for such." Office Action at page 3. The PTO arguments at pages 2-6 of the Office Action appear to reflect two issues. The first issue is an alleged lack of support for a dsRNA 21 nucleotides in length. And the second issue is an alleged lack of support for a dsRNA of 21 nucleotides in length comprising two separate non-linked strands. Each of these issues are addressed in turn below.

Support for a dsRNA 21 nucleotides in length.

The PTO quoted In re Wertheim as stating that "[w]here it is clear, for instance, that the broad described range pertains to a different invention than the narrower (and subsumed) claimed range, then the broader range does not describe the narrower range." Office Action at page 4. The PTO concluded that a 21 nucleotide long dsRNA represents a different invention from dsRNAs 15-49 nucleotides in length, and therefore In re Wertheim does not support Applicants' position that a 21 nucleotide long dsRNA is supported by the specification. Office Action at page 6. In response to Applicants' previous statements explaining that the presently pending claim length of 21 nucleotides solves the same problem as the original range of 15-49 nucleotides and that the currently claimed dsRNAs do not represent a different invention,

the PTO reiterated the assertion that "the 21 nucleotide dsRNA of the present claims is considered to be an invention distinct from the previously claimed dsRNAs for the reasons set forth in the rejection." As described below, Applicants disagree with the PTO's conclusion.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the thing claimed. See, *e.g.*, Moba, B.V. v. Diamond Automation, Inc., 325 F. 3d 1306, 1319 (Fed. Cir. 2003), and Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563. See also MPEP 2163(I). Indeed, the present specification shows one of ordinary skill in the art that Applicants' were in possession of a 21 nucleotide long dsRNA at the priority filing date of the application. The specification (and the priority application PCT/DE00/00244) explicitly recites a dsRNA of 21 nucleotides in length at Example 2 at page 17, lines 9-12, and in SEQ ID NO:8. The conclusion that one of ordinary skill would not immediately understand Applicants' possession of a dsRNA 21 nucleotides long ignores the plain language of the specification and incorrectly imposes a lack of common sense and logic upon the person of ordinary skill. One of ordinary skill in the art would have immediately recognized this disclosure and would have understood that Applicants were in possession of a 21 nucleotide long dsRNA.

The PTO stated that In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 96 (CCPA 1976) has been relied on to provide support for the limitation that the dsRNA is 21 nucleotides. Office Action at page 5. Applicants submit that In re Wertheim is not relevant, because the instant claims are directed to a dsRNA of a specific length (21 nucleotides), whereas In re Wertheim was about claiming ranges. In In re Wertheim, a disclosed internal point was combined with a disclosed end point of a first range to provide a second range. The facts of the present case are different. No range is claimed. Rather, a single length, 21 nucleotides, is claimed. As discussed above, that length is expressly disclosed in the specification. The arguments regarding In re Wertheim are therefore not relevant.

The PTO's argument that Elbashir *et al.* discloses that dsRNAs longer than 30 nucleotides were undesirable is irrelevant. While not conceding that In re Wertheim is relevant to the present situation, Applicants note that dsRNAs longer than 30 nucleotides are not a "different invention" in the sense of In re Wertheim. "Different" as used in this context means undisclosed. In re Wertheim provides that if the narrower range amounts to a new undisclosed invention then there is of course no written description. But this cannot invalidate the basic standard for written description, which is whether the specification puts one of ordinary skill in the art in possession. The specification teaches the length range of 15-49 nucleotides, as well as the 21 nucleotide embodiment, and gives reasons for designing dsRNAs in the 15-49 length range as well as a dsRNA 21 nucleotides in length. Here, the specification places one of ordinary skill in possession of the claimed length of 21 nucleotides.

In view of the foregoing, there is adequate written description support in the specification for a dsRNA 21 nucleotides in length.

Support for a 21-mer having non-linked strands. The PTO stated that "applicants clearly consider the chemical linkage an essential element for successfully inhibiting gene expression with a 21 nucleotide dsRNA," citing the sentence in the specification at page 19, lines 15-18: "this result demonstrates that even shorter dsRNAs can be used for specifically inhibiting gene expression in mammals when the double strands are stabilized by chemically linking the strands." See the Office Action at pages 5-6. Applicants respectfully disagree with the PTO's interpretation of the sentence at page 19, lines 15-18, of the specification.

Applicants maintain that the specification, plainly on its face, shows possession of 21 nucleotide dsRNAs lacking a linkage. The example at page 17, lines 9-27, provides an example of a dsRNA 21 nucleotides in length. While in that embodiment, the strands of the dsRNA are linked, elsewhere, the specification makes it quite clear that the strands can be non-linked, as currently claimed. The quoted sentence at page 19, lines 15-18, is an observation relating to the specific embodiment described at Example 2. It is not a limitation imposed on the specification as a whole. Nowhere in the specification is there a statement that linked strands are

particularly preferred for dsRNAs of any particular length. The specification supports dsRNAs 15-49 nucleotides in length, *e.g.*, 21 nucleotides in length, and supports a dsRNA of any length within the 15-49 nucleotide range (*e.g.*, 21 nucleotides) that is linked or non-linked.

The specification provides dsRNAs of several topologies, including non-linked strands, linked strands, and hairpin configurations. It is quite clear that the application conveys possession of dsRNAs having non-linked strands. For example, at page 4, line 26, of the specification, it is disclosed that "the double-stranded structure is formed by two separate RNA strands or by autocomplementary regions..." Furthermore, the application discloses that dsRNA, composed of separate strands, can have an additional linker. For example, the paragraph spanning pages 4 and 5 of the specification states that "to inhibit dissociation in a particularly effective fashion, the cohesion of the complementary region II, which is caused by the nucleotide pairs can be increased by at least one, preferably two, further chemical linkages." Emphasis added. Nowhere in the specification is there a statement that the optional chemical linker is more or less appropriate for a dsRNA of any particular length or length range.

Review of written description must be conducted from the standpoint of one of ordinary skill in the art. MPEP 2163(II)(A)(2). One of ordinary skill in the art would not read the specification to suggest that the optional chemical linkage should be used with dsRNAs of any particular length. Rather, one of ordinary skill would read the specification to disclose that a chemical linkage may be used with any dsRNA disclosed in the application.

The presence of the chemical linkage in the 21 nucleotide example does not eliminate from the scope of conception of the originally filed invention the embodiment of "linked and non-linked dsRNA." The linkage in the 21 nucleotide example is simply an exemplification of a single embodiment. Applicants have used one of the features of this embodiment, strand length of 21 nucleotides, to provide support for the amended length limitation of 21 nucleotides. There is nothing in the Example that suggests that the only way Applicants viewed that such agents could be made and used were as chemically linked molecules (as suggested by the Examiner). It is clear that the inventors contemplated that additional chemical linkages were optional elements.

In the present pending claims, the pertinent feature of length, 21 nucleotides, is distinct from and separate from the other disclosed limitations, such as linked versus non-linked.

The conclusion that one of ordinary skill would not immediately understand the specification to disclose both linked and non-linked embodiments of the lengths disclosed (*e.g.*, 21 nucleotides), ignores the plain language of the specification, and incorrectly imposes a lack of common sense and logic upon the person of ordinary skill. One of ordinary skill in the art would have immediately recognized this disclosure and would have understood that Applicants were in possession of an unlinked 21 nucleotide long dsRNA.

Given the disclosure of the specification and the level of skill in the art, it is clear that the specification conveys possession of the claimed invention.

As noted above, a dsRNA 21 nucleotides in length, and having non-linked strands, is also disclosed in priority application PCT/DE00/00244. Therefore, the claims are supported at least by the specification of the priority application, filed January 29, 2000. The present application is therefore at least entitled to the priority filing date of January 29, 2000.

In view of the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 4 and 6-9 under 35 U.S.C. § 112, first paragraph, for failure to satisfy the written description requirement.

35 U.S.C. § 102

Claims 4 and 6-9 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Elbashir (2001) and under 35 U.S.C. § 102(e) as being anticipated by Tuschl *et al.* (WO 02/44321).

The PTO maintains these rejections based on the incorrect priority date of July 2, 2003. As discussed above, Applicants are entitled to the priority date of PCT/DE00/00244, filed January 29, 2000. Elbashir *et al.* and Tuschl *et al.* are therefore not available as prior art, and Applicants respectfully request that the rejections under 35 U.S.C. § 102 be withdrawn.

35 U.S.C. § 103

Claims 16-18 were rejected under 35 U.S.C. § 103 as being unpatentable over Agrawal *et al.* (WO 94/01550, of record). Applicants respectfully traverse the rejection.

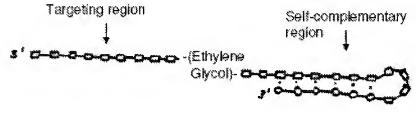
Agrawal *et al.* teaches oligonucleotides useful for antisense therapeutics that comprise (i) a target hybridizing region and (ii) a self-complementary region. Agrawal *et al.* does not teach or suggest a dsRNA 21 nucleotides in length having a complementary region within the dsRNA formed by two separate RNA single strands as required by the claims.

Agrawal *et al.* is clearly about oligonucleotides having a hairpin structure, for the purpose of rendering the oligonucleotide resistant to degradation, and not about oligonucleotides comprising two separate and complementary RNA strands. Agrawal *et al.* states at page 5, lines 2-4, that "[t]he invention relates to novel therapeutic agents used in the antisense oligonucleotide therapeutic approach…Oligonucleotides according to the invention form stable hybrids with target sequences under physiological conditions, activate RNase H and produce only nucleosides as degradation product." See also figure 1, and the corresponding description at page 7, which illustrates a self-stabilizing oligonucleotide according to the invention in hairpin configuration and hybridized to a target sequence. One having ordinary skill in the art would not read Agrawal *et al.* to suggest an oligoribonucleotide consisting of two separate complementary oligoribonucleotide strands (dsRNA).

Agrawal *et al.* teaches "self-complementary" oligonucleotides. Agrawal at page 8, lines 22-24, states that "[o]ligonucleotides according to the invention are generally characterized by having two regions: a target hybridizing region and a self-complementary region." Agrawal *et al.* at page 15, lines 1-6, states: "The second significant region of self-stabilized oligonucleotides according to the invention is the self-complementary region. The self-complementary region contains oligonucleotide sequences that are complementary to other oligonucleotide sequences within the oligonucleotide," (emphasis added) (*i.e.*, within the same oligonucleotide). Agrawal *et al.* further states at page 15, lines 9-11, that "[t]he complementary sequences form base pairs, resulting in the formation of a hairpin structure, as shown in Figure 1, or a hammer-like structure, as shown in Figure 2" (emphasis added). Thus, self-complementary

oligonucleotides require a single oligonucleotide that folds back on and hybridizes to itself. "Self-complementary" does not mean two separate oligonucleotides that hybridize to each other.

Agrawal *et al.* at page 15, lines 31-36, states: "In one preferred embodiment the self-complementary region may be connected to the target hybridizing region by a suitable non-nucleic acid linker," *e.g.,* an (ethylene glycol)1-6 linker. Such an arrangement still requires the self-complementary region to be on a single oligonucleotide, and never formed from two separate oligonucleotides, as required by claims 16-18. In the embodiment contemplated by Agrawal *et al.*, (i) the target hybridizing region (*i.e.*, the antisense strand) is on one oligonucleotide, and (ii) the hairpin structure (or hammer-like structure) is on a separate oligonucleotide. Such an arrangement would look like the following (for example):



As described by Agrawal *et al.*, a linker would only be used to connect the targeting region of the oligonucleotide with the self-complementary region, not to connect two separate complementary strands, as required by claims 16-18.

The PTO relies on KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007), for guidance in applying the standard under 35 U.S.C. § 103. The Supreme Court in KSR noted that

> to determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the market place; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit.

KSR at 1731 (emphasis added). Further, the key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2141(III) and MPEP 2143. Agrawal *et al.* goes to great lengths to explain that the self-complementary oligonucleotides described in the reference are advantageous, because such an arrangement protects against degradation (see, *e.g.*, Agrawal *et al.* at page 5, lines 22-33, and at page 8, line 32, to page 9, line 3). There is nothing in Agrawal *et al.* to suggest an oligoribonucleotide consisting of two separate complementary oligoribonucleotide strands of any length whatsoever, let alone the 21 nucleotides required by the claims. The PTO fails to articulate a reason why one of ordinary skill in the art would modify the self-complementary oligonucleotides of Agrawal *et al.* to arrive at the claimed dsRNAs.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

Applicants believe the claims are in condition for allowance, and a notice to this effect is respectfully requested.

No fees are believed to be due. Any necessary charges, or any credits, should be applied to Deposit Account No. 50/2762, referencing Attorney Docket No. A2038-706120.

Respectfully submitted,

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/Allyson R. Hatton/
Allyson R. Hatton, Ph.D.
Reg. No. 54,154

PTO Customer No. 76634
LOWRIE, LANDO & ANASTASI, LLP
One Main Street
Cambridge, Massachusetts 02142
United States of America
Telephone: 617-395-7000
Facsimile: 617-395-7070